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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,327	04/27/2000	Mathew John During	40174	1919

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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1633	9

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/559,327	DURING, MATHEW JOHN	
	Examiner	Art Unit	
	Brian Whiteman	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1633.

The terminal disclaimer and the amendment filed on 10/4/01 paper nos. 8 and 7 respectively are acknowledged.

Amendment of claim 12 and specification is acknowledged in paper no. 7 filed on 10/4/01 is acknowledged.

Cancellation of claims 7 and 9 in paper no. 7 filed on 10/4/01 is acknowledged.

Applicant's arguments filed October 4, 2001 have been fully considered.

Claims 1-6, 8, and 10-12 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of expressing a gene product in the gastrointestinal tract (GI) of an animal, which comprises: delivering a recombinant AAV vector through an oro-gastric tube to the proximal end of the animal's intestine, wherein said vector comprises a gene encoding a protein; 2) The method of 1, wherein said gene is operably linked to a promoter operable in said GI and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention encompasses oral delivery of a recombinant adeno-associated virus comprising a heterologous gene, wherein expression of said gene is observed in the gastrointestinal (GI) tract of a mammal.

The state of the art at the time the application was filed and currently for oral gene delivery was considered unpredictable as exemplified by Page et al., DDT, and Vol. 6, 2001, pages 92-101, Page teaches that:

> To date, most gene delivery strategies have concentrated on the parenternal route of delivery and oral administration has been largely ignored. This is mainly due to the large hurdles that need to be overcome for oral gene delivery, such as acid pH in the stomach, the nucleases, lipases, and the poor permeability of both genes and gene vectors across the intestinal epithelium owing to the size and charge of the gene delivery vehicles. As a result of these factors, the greatest challenge faced by oral gene therapy is achieving delivery of sufficient genetic material in the correct cell types to produce therapeutic or prophylactic protein expression levels (page 92).

Furthermore, Page teaches:

> Despite the fact that somatic gene therapy to the intestine was suggested in 1992, it has not been seriously investigated until recently. This was primarily because of the low oral bioavailability of the available DNA vector systems and also the relatively few genetic disorders directly associated with the GI tract (e.g. familial adenomatous polyposis, cystic fibrosis and various colon cancers. See page 93.

Thus, the level of skill in the art for oral gene delivery was considered unpredictable.

The disclosure teaches using an oro-gastric tube for delivering a recombinant AAV vector comprising a gene encoding β-galactosidase to a rat model of lactose intolerance, which resulted in the phenotypic correction of rats with lactose intolerance (pages 14-17).

However, with respect with respect to claims 1-6, 8, 10-12, which encompass several routes of administration, especially oral ingestion or suppository, the disclosure, in view of the In re Wands Factors, fails to provide sufficient guidance for any other route of administration other than using an oro-gastric tube for administering AAV vectors to a mammal. The specification uses an oro-gastric tube for administering AAV to mice, however, the specification describes the position of tube at the proximal end of the intestine (page 11), which one skilled in the art would reasonably determine, absence evidence to the contrary, that the oro-gastric tube bypasses the stomach and the AAV vectors are directly administered to the small intestine. In view of the art of record and the lack of sufficient guidance provided by the as-filed specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from using an oro-gastric tube to avoid the anatomic and physiologic barriers of an animal, which include mucus (entraps foreign pathogens), gastric acidity, and interferons, to administer said vector to

an animal. In view of the doubts expressed in the art of record by Page and the amount of direction or guidance presented by the specification, which fails to provide sufficient guidance for one skilled in the art to reasonably extrapolate from using an oro-gastric tube to using any other route of administration of AAV vectors to a mammal. At the time the application was filed, oral gene therapy was considered not enabled because of the large hurdles that need to be overcome for oral gene delivery. See Page, pages 92-93.

Furthermore, with respect to claims 1, 10 and 11, which encompass expressing a gene product in the gut of an animal. One skilled in the art would understand that the claims read on an in vivo therapeutic method of gene therapy. Specifically, the claimed invention encompasses expressing a gene product in humans. The state of the art for gene therapy at the time the application was filed and currently as exemplified by Rubanyi (Molecular Aspect of Medicine, Vol. 22, 2001, pages 113-142) teaches that:

> The most promising areas for gene therapy today are hemophilias and cardiovascular diseases. This is based on the relative ease of access of blood vessels for gene therapy, and also because existing gene delivery technologies may be sufficient to achieve effective therapeutic benefits for some of these indication (transient expression in some but not all affected cells is required to achieve a therapeutic effect at a relatively low does of vector) (abstract). For other diseases (including cancer) further development in gene delivery vectors and gene expression systems will be required. It is important to note, that there will not be a universal vector and each clinical indication may require a

specific set of technical hurdles to overcome. These will include modification of viral vectors, engineering of non-viral vectors by mimicking the beneficial properties of viruses, cell-based gene delivery technologies, and development of innovative gene expression regulation systems (abstract).

As stated before, the disclosure teaches using an oro-gastric tube for delivering a recombinant AAV vector comprising a gene encoding β-galactosidase to a rat model of lactose intolerance, which resulted in the phenotypic correction of rats with lactose intolerance (pages 14-17).

The as-filed specification and the state of the art fail to provide sufficient guidance for one skilled in the art to reasonably extrapolate from treating lactose intolerance, which does not require precise gene regulation to any other disorder that requires precise gene regulation. The art of record expresses concerns with using one particularly vector (e.g. AAV) for treating any disorder and/or any disease in any mammal since there will not be a universal vector for treating any disease or any disorder in any mammal. Furthermore, the state of the art at the time the application was filed and the specification fail to provide sufficient guidance for one skilled in the art of gene therapy for how to treat any GI disorder or any disease that requires precise gene regulation (e.g. diabetes) other than disorders that do not require precise gene regulation (e.g. lactose intolerance) in any mammal. Thus, in view of the In re Wands Factors, listed above, the quantity of experimentation required to determine the oral delivery route of a nucleic acid encoding a therapeutic protein and how to treat a genetic disorder that requires precise regulation of gene expression, and the working examples encompass treating lactose intolerance in a rat model; the as-filed specification provide sufficient guidance for how to treat any genetic disorder

and/or any disease that requires does not require precise gene regulation in the GI of any mammal and does not specification provide sufficient guidance for how to treat any genetic disorder and/or any disease that requires precise gene regulation in the GI of any mammal.

At best the disclosure is enabled for 1) A method of expressing a gene product in the gastrointestinal tract (GI) of an animal, which comprises: delivering a recombinant AAV vector through an oro-gastric tube to the proximal end of the animal's intestine, wherein said vector comprises a gene encoding a protein; 2) The method of 1, wherein said gene is operably linked to a promoter operable in said GI.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1-2 listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the application was filed, and given the lack of sufficient guidance as to a gene therapy effect produced by any AAV vector cited in the claims for treating any disorder or any disease that does require precise gene regulation other than treating a mammal with any GI disorder or disease that does not require precise gene regulation, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

With respect to applicant's traversal paper no. 7, 10/4/01, pages 3-5.

Applicant's traverse that: 1) Applicant argues that the enablement requirement is met if the description enables any mode of making and using the claimed invention (see In re Wright or Engel Industries, Inc. V. Lockformer Co.).

Applicant's traversal with respect to issue 1 is not found persuasive. First, In re Wright is not applicable to the pending application because In re Wright is a case that encompasses a vaccine for treating RNA pathogens. In addition, the Engel Industries case encompasses royalty issues. Neither case addresses any of the issues set forth concerning the unpredictability of gene therapy and the oral delivery of an AAV vector to any mammal. In addition, the applicant does not provide sufficient guidance for any improvement over the state of the art concerning the unpredictability of gene therapy other than using an oro-gastric tube to avoid the stomach for delivering AAV to the GI of a mammal.

Applicant's traverse that: 2) Applicant argues that administration of AAV by routes that offer more direct access to the circulation or target tissue were known in the prior art.

Applicants' assertion with respect to issue 2 is not found persuasive. First, the patents cited in applicant's traversal encompass intra-arterially, intravenous, and stereotactic administration into the brain, none of these routes of administration can be reasonably correlated to a therapeutic method of oral gene delivery of an AAV vector. The state of the art at the time the application was filed and currently display that there is no evidence of expression of oral administered genes by the RT-PCR method, see Hohlweg et al. Mol. Genet. Genomics, Vol. 265, pp. 225-233, 2001. Also, Hohlweg states, "Information on the stability and persistence of macromolecules in the intestinal system has previously not been available (page 225)." In view of the art of record, the applicants do not provide sufficient guidance for any improvement over the state of the art concerning the unpredictability of oral gene therapy as exemplified in the art of record other than using an oro-gastric tube to avoid the stomach.

Applicant's traverse that: 3) AAV infects a wide range of cells as exemplified Dreizin et al and During et al.

Applicants' assertion with respect to issue 3 is not found persuasive. First, Dreizin does not teach one skilled in the art how to reasonably correlate expression of B-Gal in the spleen, liver, intestines, and kidney to a therapeutic method of in oral gene therapy in any of these organs. Furthermore, Dreizin does not address any of the issues set forth concerning the unpredictability of oral gene therapy. In addition, the During (applicant's own work) does not provide sufficient guidance for any improvement over the state of the art concerning the unpredictability of oral gene therapy other than using an oro-gastric tube to avoid the stomach for administering AAV to a mammal. Furthermore, During states, "analysis of other organs using PCR showed the vector did not disseminate beyond the GI tract (page 1132)."

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1633
November 30, 2001

DAVE T. NGUYEN
PRIMARY EXAMINER